(b) a protein with an N-terminal amino acid that is not a cysteine appended with at least one hydrophobic moiety; and

(c) a protein with at least one hydrophobic moiety substituted for the N-terminal amino acid, wherein the protein, in the absence of the hydrophobic moiety, binds to a receptor or coreceptor, and the hydrophobic moiety does not substantially affect binding affinity of the protein to the receptor or coreceptor.

2. The protein of claim 1, wherein the hydrophobic moiety is a peptide comprising at least one hydrophobic amino acid.

3. The protein of claim 1, wherein the hydrophobic moiety is a lipid.

4. The protein of claim 1, wherein the protein further comprises a hydrophobic moiety substituted for, or appended to, the C-terminal amino acid.

5. The protein of claim 1, wherein the protein is an extracellular signaling protein.

6. The protein of claim 1, wherein the N-terminal amino acid is a functional derivative of a cysteine.

7. The protein of claim 1, wherein the protein is modified at both the N-terminal amino acid and the C-terminal amino acid.

8. (Amended) The protein of claims 4 or 7, wherein the protein has a hydrophobic moiety substituted for, or appended to, at least one internal amino acid.

9. The protein of claim 1, wherein the protein has a hydrophobic moiety substituted for, or appended to, at least one amino acid intermediate to the N-terminal and C-terminal amino acids.

10. The protein of claim 3, wherein the lipid moiety is a fatty acid selected from saturated and unsaturated fatty acids having between 2 and 24 carbon atoms.

14. The protein of claim 1, further comprising a vesicle in contact with the hydrophobic moiety.

a3

15. (Amended) The protein of claim 14, wherein the vesicle is selected from a cell membrane, a micelle, and a liposome.

19. An isolated, protein of the form: A-Cys-[Sp]-B- [Sp]- X, wherein

A is a hydrophobic moiety;

Cys is a cysteine or functional equivalent thereof;

[Sp] is an optional spacer peptide sequence;

B is a protein comprising a plurality of amino acids and, optionally, another spacer peptide sequence; and

X is optionally another hydrophobic moiety linked to an amino acid of protein B.

22. The isolated protein of claim 19, wherein protein B is modified at at least one other amino acid with at least one hydrophobic moiety.

23. The isolated protein of claim 19, wherein the A-Cys linkage is via an amino group of cysteine.

24. The isolated protein of claim 19, further comprising a vesicle in contact therewith.

a4

25. (Amended) The isolated protein of claim 24, wherein the vesicle in contact therewith is selected from a cell membrane, micelle, and liposome.

26. A vesicle to which is attached a plurality of molecules, at least two of the plurality having the form of claim 19.

a5

27. (Amended) The vesicle of claim 26, wherein the vesicle is selected from a cell membrane, liposome, and micelle.

28. (Amended) An isolated protein having a C-terminal amino acid and an N-terminal thioproline group, said group formed by reacting an aldehyde with an N-terminal cysteine of the protein, wherein the protein, in the absence of the thioproline group, binds to a receptor or coreceptor, and the thioproline group does not substantially affect binding affinity of the protein to the receptor or coreceptor.

29. (Amended) An isolated protein having a C-terminal amino acid and an N-terminal amide group, said group formed by reacting a fatty acid thioester with an N-terminal cysteine of the protein, wherein the protein, in the absence of the amide group, binds to a receptor or coreceptor, and the amide group does not substantially affect binding affinity of the protein to the receptor or coreceptor.

30. (Amended) An isolated protein having a C-terminal amino acid and an N-terminal maleimide group, said N-terminal maleimide group formed by reacting a maleimide group with the N-terminal cysteine of the protein, wherein the protein, in the absence of the maleimide group, binds to a receptor or coreceptor, and the maleimide group does not substantially affect binding affinity of the protein to the receptor or coreceptor.

31. (Amended) The isolated protein of claims 28, 29 or 30, wherein the C-terminal amino acid of the protein is modified with ~~an~~ hydrophobic moiety.

34. (Amended) A method of generating a multivalent protein complex comprising the step of linking, in the presence of a vesicle, a hydrophobic moiety to an N-terminal cysteine of a protein, or a functional equivalent of the N-terminal cysteine, wherein the protein, in the absence of the hydrophobic moiety, binds to a receptor or coreceptor, and the hydrophobic moiety does not substantially affect binding affinity of the protein to the receptor or coreceptor.

35. The method of claim 34, wherein the step of linking comprises linking a lipid moiety which is selected from saturated and unsaturated fatty acids having between 2 and 24 carbon atoms.

39. (Amended) The method of claim 34, wherein the step of linking comprises linking with a vesicle selected from a cell membrane, liposome and micelle.

a7 Amend C4

40. (Amended) A method for modifying a physico-chemical property of a protein, comprising introducing at least one hydrophobic moiety to an N-terminal cysteine of the protein or to a functional equivalent of the N-terminal cysteine, wherein the protein, in the absence of the hydrophobic moiety, binds to a receptor or coreceptor, and the hydrophobic moiety does not substantially affect binding affinity of the protein to the receptor or coreceptor.

41. The method of claim 40, further comprising contacting the hydrophobic moiety with a vesicle.

42. The method of claim 40, wherein the hydrophobic moiety is either a lipid moiety selected from saturated and an unsaturated fatty acids having between 2 and 24 carbon atoms or is a hydrophobic protein.

a8 46. (Amended) The method of claim 41, wherein the step of contacting comprises contacting with a vesicle selected from a cell membrane, liposome and micelle.

47. A protein complex, produced by the method of claim 34.

48. A modified protein, produced by the method of claim 40.

a9 49. (Amended) The complex of claim 47, wherein the protein is selected from gelsolin, an interferon, an interleukin, tumor necrosis factor, monocyte colony stimulating factor, granulocyte colony stimulating factor, granulocyte macrophage colony stimulating factor, erythropoietin, platelet derived growth factor, growth hormone, and insulin.

Amend C5

50. (Amended) A method for modifying a protein having a biological activity and containing an N-terminal cysteine, comprising reacting the N-terminal cysteine with a fatty acid thioester to form an amide, wherein such modification enhances the protein's biological activity, wherein the protein, in the absence of the modification, binds to a receptor or coreceptor, and the

modification does not substantially affect binding affinity of the protein to the receptor or coreceptor.

53. (Amended) A method for modifying a protein having a biological activity and containing an N-terminal cysteine, comprising reacting the N-terminal cysteine with a maleimide group, wherein the protein, in the absence of the maleimide group, binds to a receptor or coreceptor, and the maleimide group does not substantially affect binding affinity of the protein to the receptor or coreceptor, and wherein such modification enhances the protein's biological activity.

56. (Amended) A method for modifying a protein that binds to an extracellular receptor, comprising appending a hydrophobic peptide to the protein, wherein the protein has a biological activity and the hydrophobic peptide enhances the biological activity.

57. (Amended) The method of claim 56, wherein the hydrophobic peptide is appended to an amino acid of the protein selected from the N-terminal amino acid, the C-terminal amino acid, an amino acid intermediate between the N-terminal amino acid, and the C-terminal amino acid, and combinations of the foregoing.

60. A therapeutic use of the protein of any of claims 1 or 20, comprising administering the protein to a subject.

61. A method of treating a neurological disorder in a patient comprising administering to the patient a protein of any of claims 1 or 20.

62. The protein of claim 1, wherein the protein is an extracellular signaling protein.

63. The method of claim 57, wherein the step of appending comprises replacing at least the N- terminal amino acid of the protein with at least one hydrophobic amino acid.

64. The method of claim 63, wherein the at least one hydrophobic amino acid is a plurality of isoleucine residues.

65. The method of claim 63, further comprising chemically modifying at least one of the isoleucine residues.

66. (Amended) An isolated protein having a C-terminal amino acid and an N-terminal acetamide group, said group formed by reacting a substituted acetamide with an N-terminal cysteine of the protein, wherein the protein, in the absence of the acetamide group, binds to a receptor or coreceptor, and the hydrophobic moiety does not substantially affect binding affinity of the protein to the receptor or coreceptor.

67. (Amended) An isolated protein having a C-terminal amino acid and an N-terminal thiomorpholine group, said group formed by reacting a haloketone group with an N-terminal cysteine of the protein, wherein the protein, in the absence of the thiomorpholine group, binds to a receptor or coreceptor, and the thiomorpholine group does not substantially affect binding affinity of the protein to the receptor or coreceptor.

68. (Amended) A method for modifying a protein that binds to an extracellular receptor and contains an N-terminal cysteine, comprising reacting the N-terminal cysteine with a substituted acetamide group, wherein such modification enhances the protein's biological activity, wherein the protein has a biological activity, and the acetamide group enhances the biological activity of the protein.

71. (Amended) A method for modifying a protein having a biological activity and containing an N-terminal cysteine, comprising reacting the N-terminal cysteine with a haloketone group, wherein such modification enhances the protein's biological activity, wherein the protein, in the absence of the haloketone group, binds to a receptor or coreceptor, and the haloketone group does not substantially affect binding affinity of the protein to the receptor or coreceptor.

87. (Amended) A method for modifying a protein that binds an extracellular receptor, comprising treating the protein with an active thioester under conditions sufficient to acylate the protein, wherein the protein has a biological activity, and the hydrophobic moiety enhances the biological activity of the protein.

88. (Amended) The method of claim 87, wherein the protein is acylated at an amino acid selected from the N-terminal amino acid, the C-terminal amino acid, an amino acid intermediate between the N-terminal amino acid and the C-terminal amino acid, and combinations of the foregoing.

~~90.~~ 89 (Amended) A method for modifying a protein that binds an extracellular receptor and contains an N-terminal cysteine, comprising reacting the N-terminal cysteine with a fatty acid active thioester to form an amide, wherein the protein has a biological activity, and the modification enhances the biological activity of the protein.

~~91.~~ 90 (Amended) A method of generating a multivalent protein complex comprising the step of linking, in the presence of a vesicle, a hydrophobic moiety to an N-terminal cysteine of a protein, or a functional equivalent of the N-terminal cysteine, using an active thioester, wherein the protein, in the absence of the hydrophobic moiety, binds to a receptor or coreceptor, and the hydrophobic moiety does not substantially affect binding affinity of the protein to the receptor or coreceptor.

~~92.~~ 91 The method of claim ~~91~~ 90, wherein the step of linking comprises linking a lipid moiety which is selected from saturated and unsaturated fatty acids having between 2 and 24 carbon atoms.

~~93.~~ 92 The method of claim ~~91~~ 90, wherein the hydrophobic moiety is either a lipid moiety selected from saturated and an unsaturated fatty acids having between 2 and 24 carbon atoms or is a hydrophobic protein.

Please add the following new claims:

~~94.~~ 93 (New) An isolated polypeptide ligand for an extracellular receptor, wherein the ligand is covalently attached to a hydrophobic moiety that enhances the biological activity of the ligand relative to the biological activity of the ligand in the absence of the hydrophobic moiety.

95. (New) The protein of claim 94, wherein the hydrophobic moiety is a peptide comprising at least one hydrophobic amino acid.

96. (New) The protein of claim 94, wherein the hydrophobic moiety is a lipid.

97. (New) The protein of claim 94, wherein the protein further comprises a hydrophobic moiety substituted for, or appended to, the C-terminal amino acid.

98. (New) The protein of claim 94, wherein the protein is an extracellular signaling protein.

99. (New) The protein of claim 94, wherein the N-terminal amino acid is a functional derivative of a cysteine.

100. (New) The protein of claim 94, wherein the protein is modified at both the N-terminal amino acid and the C-terminal amino acid.

101. (New) The protein of claim 97 or 100, wherein the protein has a hydrophobic moiety substituted for, or appended to, at least one internal amino acid.

102. (New) The protein of claim 94, wherein the protein has a hydrophobic moiety substituted for, or appended to, at least one amino acid intermediate to the N-terminal and C-terminal amino acids.

103. (New) The protein of claim 96, wherein the lipid moiety is a fatty acid selected from saturated and unsaturated fatty acids having between 2 and 24 carbon atoms.

104. (New) The protein of claim 94, further comprising a vesicle in contact with the hydrophobic moiety.

105. (New) The protein of claim 104, wherein the vesicle is selected from a cell membrane, a micelle, and a liposome.

The claims presented above incorporate changes as indicated by the marked-up versions below.

1. (Amended) An isolated~~,~~ protein comprising an N-terminal amino acid and a C-terminal amino acid, wherein the protein is selected from ~~the group consisting of~~:

(a) a protein with an N-terminal cysteine that is appended with at least one hydrophobic moiety;

(b) a protein with an N-terminal amino acid that is not a cysteine appended with at least one hydrophobic moiety; and

(c) a protein with at least one hydrophobic moiety substituted for the N-terminal amino acid, wherein the protein, in the absence of the hydrophobic moiety, binds to a receptor or coreceptor, and the hydrophobic moiety does not substantially affect binding affinity of the protein to the receptor or coreceptor.

2. The protein of claim 1, wherein the hydrophobic moiety is a peptide comprising at least one hydrophobic amino acid.

3. The protein of claim 1, wherein the hydrophobic moiety is a lipid.

4. The protein of claim 1, wherein the protein further comprises a hydrophobic moiety substituted for, or appended to, the C-terminal amino acid.

5. The protein of claim 1, wherein the protein is an extracellular signaling protein.

6. The protein of claim 1, wherein the N-terminal amino acid is a functional derivative of a cysteine.

7. The protein of claim 1, wherein the protein is modified at both the N-terminal amino acid and the C-terminal amino acid.

8. (Amended) The protein of claims 4 or 7, wherein the protein has a hydrophobic moiety substituted for, or appended to, at least one internal amino acid~~, e.g., intermediate to the N-terminal and C-terminal amino acids~~.

9. The protein of claim 1, wherein the protein has a hydrophobic moiety substituted for, or appended to, at least one amino acid intermediate to the N-terminal and C-terminal amino acids.

10. The protein of claim 3, wherein the lipid moiety is a fatty acid selected from saturated and unsaturated fatty acids having between 2 and 24 carbon atoms.

14. The protein of claim 1, further comprising a vesicle in contact with the hydrophobic moiety.

15. (Amended) The protein of claim 14, wherein the vesicle is selected from ~~the group consisting of~~ a cell membrane, a micelle, and a liposome.

19. An isolated, protein of the form: A-Cys-[Sp]-B- [Sp]- X, wherein
A is a hydrophobic moiety;
Cys is a cysteine or functional equivalent thereof;
[Sp] is an optional spacer peptide sequence;
B is a protein comprising a plurality of amino acids and, optionally, another spacer peptide sequence; and
X is optionally another hydrophobic moiety linked to an amino acid of protein B.

22. The isolated protein of claim 19, wherein protein B is modified at at least one other amino acid with at least one hydrophobic moiety.

23. The isolated protein of claim 19, wherein the A-Cys linkage is via an amino group of cysteine.

24. The isolated protein of claim 19, further comprising a vesicle in contact therewith.

25. (Amended) The isolated protein of claim 24, wherein the vesicle in contact therewith is selected from ~~the group consisting of~~ a cell membrane, micelle, and liposome.

26. A vesicle to which is attached a plurality of molecules, at least two of the plurality having the form of claim 19.

27. (Amended) The vesicle of claim 26, wherein the vesicle is selected from ~~the group consisting of~~ a cell membrane, liposome, and micelle.

28. (Amended) An isolated~~,~~ protein having a C-terminal amino acid and an N-terminal thioproline group, said group formed by reacting an aldehyde with an N-terminal cysteine of the protein, wherein the protein, in the absence of the thioproline group, binds to a receptor or coreceptor, and the thioproline group does not substantially affect binding affinity of the protein to the receptor or coreceptor.

29. (Amended) An isolated~~,~~ protein having a C-terminal amino acid and an N-terminal amide group, said group formed by reacting a fatty acid thioester with an N-terminal cysteine of the protein, wherein the protein, in the absence of the amide group, binds to a receptor or coreceptor, and the amide group does not substantially affect binding affinity of the protein to the receptor or coreceptor.

30. (Amended) An isolated~~,~~ protein having a C-terminal amino acid and an N-terminal maleimide group, said N-terminal maleimide group formed by reacting a maleimide group with the N-terminal cysteine of the protein, wherein the protein, in the absence of the maleimide group, binds to a receptor or coreceptor, and the maleimide group does not substantially affect binding affinity of the protein to the receptor or coreceptor.

31. (Amended) The isolated protein of claims 28, 29 or 30, wherein the C-terminal amino acid of the protein is modified with ~~an~~ hydrophobic moiety.

34. (Amended) A method of generating a multivalent protein complex comprising the step of linking, in the presence of a vesicle, a hydrophobic moiety to an N-terminal cysteine of a protein,

or a functional equivalent of the N-terminal cysteine, wherein the protein, in the absence of the hydrophobic moiety, binds to a receptor or coreceptor, and the hydrophobic moiety does not substantially affect binding affinity of the protein to the receptor or coreceptor.

35. The method of claim 34, wherein the step of linking comprises linking a lipid moiety which is selected from saturated and unsaturated fatty acids having between 2 and 24 carbon atoms.

39. (Amended) The method of claim 34, wherein the step of linking comprises linking with a vesicle selected from ~~the group consisting of~~ a cell membrane, liposome and micelle.

40. (Amended) A method for modifying a physico-chemical property of a protein, comprising introducing at least one hydrophobic moiety to an N-terminal cysteine of the protein or to a functional equivalent of the N-terminal cysteine, wherein the protein, in the absence of the hydrophobic moiety, binds to a receptor or coreceptor, and the hydrophobic moiety does not substantially affect binding affinity of the protein to the receptor or coreceptor.

41. The method of claim 40, further comprising contacting the hydrophobic moiety with a vesicle.

42. The method of claim 40, wherein the hydrophobic moiety is either a lipid moiety selected from saturated and an unsaturated fatty acids having between 2 and 24 carbon atoms or is a hydrophobic protein.

46. (Amended) The method of claim 41, wherein the step of contacting comprises contacting with a vesicle selected from ~~the group consisting of~~ a cell membrane, liposome and micelle.

47. A protein complex, produced by the method of claim 34.

48. A modified protein, produced by the method of claim 40.

49. (Amended) The complex of claim 47, wherein the protein is selected from ~~the group consisting of~~ gelsolin,; an interferon, an interleukin, tumor necrosis factor, monocyte colony stimulating factor, granulocyte colony stimulating factor, granulocyte macrophage colony stimulating factor, erythropoietin, platelet derived growth factor, growth hormone, and insulin.

50. (Amended) A method for modifying a protein having a biological activity and containing an N-terminal cysteine, comprising reacting the N-terminal cysteine with a fatty acid thioester to form an amide, wherein such modification enhances the protein's biological activity, wherein the protein, in the absence of the modification, binds to a receptor or coreceptor, and the modification does not substantially affect binding affinity of the protein to the receptor or coreceptor.

53. (Amended) A method for modifying a protein having a biological activity and containing an N-terminal cysteine, comprising reacting the N-terminal cysteine with a maleimide group, wherein the protein, in the absence of the maleimide group, binds to a receptor or coreceptor, and the maleimide group does not substantially affect binding affinity of the protein to the receptor or coreceptor, and wherein such modification enhances the protein's biological activity.

56. (Amended) A method for modifying a protein that binds to an extracellular receptor, ~~having a biological activity~~ comprising appending ~~an~~ hydrophobic peptide to the protein, wherein the protein has a biological activity and the hydrophobic peptide enhances the biological activity.

57. (Amended) The method of claim 56, wherein the hydrophobic peptide is appended to an amino acid of the protein selected from ~~the group consisting of~~ the N-terminal amino acid, the C-terminal amino acid, an amino acid intermediate between the N-terminal amino acid, and the C-terminal amino acid, and combinations of the foregoing.

60. A therapeutic use of the protein of any of claims 1 or 20, comprising administering the protein to a subject.

61. A method of treating a neurological disorder in a patient comprising administering to the patient a protein of any of claims 1 or 20.

62. The protein of claim 1, wherein the protein is an extracellular signaling protein.

63. The method of claim 57, wherein the step of appending comprises replacing at least the N- terminal amino acid of the protein with at least one hydrophobic amino acid.

64. The method of claim 63, wherein the at least one hydrophobic amino acid is a plurality of isoleucine residues.

65. The method of claim 63, further comprising chemically modifying at least one of the isoleucine residues.

66. (Amended) An isolated~~,~~ protein having a C-terminal amino acid and an N-terminal acetamide group, said group formed by reacting a substituted acetamide with an N-terminal cysteine of the protein, wherein the protein, in the absence of the acetamide group, binds to a receptor or coreceptor, and the hydrophobic moiety does not substantially affect binding affinity of the protein to the receptor or coreceptor.

67. (Amended) An isolated~~,~~ protein having a C-terminal amino acid and an N-terminal thiomorpholine group, said group formed by reacting a haloketone group with an N-terminal cysteine of the protein, wherein the protein, in the absence of the thiomorpholine group, binds to a receptor or coreceptor, and the thiomorpholine group does not substantially affect binding affinity of the protein to the receptor or coreceptor.

68. (Amended) A method for modifying a protein that binds to an extracellular receptor ~~having a biological activity~~ and contains ~~containing~~ an N-terminal cysteine, comprising reacting the N-terminal cysteine with a substituted acetamide group, wherein such modification enhances the protein's biological activity, wherein the protein has a biological activity, and the acetamide group enhances the biological activity of the protein.

71. (Amended) A method for modifying a protein having a biological activity and containing an N-terminal cysteine, comprising reacting the N-terminal cysteine with a haloketone group, wherein such modification enhances the protein's biological activity, wherein the protein, in the absence of the haloketone group, binds to a receptor or coreceptor, and the haloketone group does not substantially affect binding affinity of the protein to the receptor or coreceptor.

87. (Amended) A method for modifying a protein that binds an extracellular receptor, ~~having a biological activity~~ comprising treating the protein with an active thioester under conditions sufficient to acylate the protein, wherein the protein has a biological activity, and the hydrophobic moiety enhances the biological activity of the protein.

88. (Amended) The method of claim 87, wherein the protein is acylated at an amino acid selected from ~~the group consisting of~~ the N-terminal amino acid, the C-terminal amino acid, an amino acid intermediate between the N-terminal amino acid and the C-terminal amino acid, and combinations of the foregoing.

90. (Amended) A method for modifying a protein that binds an extracellular receptor ~~having a biological activity~~ and contains ~~containing~~ an N-terminal cysteine, comprising reacting the N-terminal cysteine with a fatty acid active thioester to form an amide, wherein ~~such modification enhances~~ the protein~~'s~~ has a biological activity, and the modification enhances the biological activity of the protein.

91. (Amended) A method of generating a multivalent protein complex comprising the step of linking, in the presence of a vesicle, a hydrophobic moiety to an N-terminal cysteine of a protein, or a functional equivalent of the N-terminal cysteine, using an active thioester, wherein the protein, in the absence of the hydrophobic moiety, binds to a receptor or coreceptor, and the hydrophobic moiety does not substantially affect binding affinity of the protein to the receptor or coreceptor.

92. The method of claim 91, wherein the step of linking comprises linking a lipid moiety which is selected from saturated and unsaturated fatty acids having between 2 and 24 carbon atoms.